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Inspections, Compliance, Enforcement, and Criminal Investigations

Agnesian Healthcare IRB 3/25/13



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

MARCH 25, 2013

WARNING LETTER

CERTIFIED MAIL RETURN RECEIPT REQUESTED

Mr. Steven Little
President and Chief Executive Officer
Agnesian Healthcare
430 East Division Street
Fond du Lac, WI 54935

Ref.: 13-HFD-45-03-01

Dear Mr. Little:

This Warning Letter informs you of unacceptable conditions observed during the U.S. Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) that was conducted between November 7, 2012, and November 13, 2012, by Ms. Denise L. Burosh, representing FDA. The purpose of this inspection was to determine whether the IRB's procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), parts 50 and 56. These regulations apply to institutions that, like Agnesian Healthcare, conduct clinical investigations of products regulated by FDA. This inspection revealed that Agnesian Healthcare's IRB has substantially failed to follow these regulations.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Burosh presented the IRB Chairman, Mr. James P. Mugan, with Form FDA 483, Inspectional Observations. We acknowledge receipt of the IRB's November 21, 2012, written response to the Form FDA 483. From our review of the FDA's establishment inspection report, the documents submitted with that report, and the IRB's written response, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We wish to emphasize the following:

1. The IRB failed to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB [21 CFR 56.108(a), 21 CFR 56.108(b), and 21 CFR

56.115(a)(6)].

In order to fulfill the requirements of the IRB regulations, each IRB must prepare, maintain, and follow written procedures describing IRB functions and operations specified in the regulations.

Agnesian Healthcare IRB provided two documents titled "Policy and Procedure" concerning the IRB's activity to FDA. The first document is subtitled "Institutional Review Board" and has an effective date of November, 2008. The second document is subtitled "Clinical Trial Screening" and has an effective date of September 17, 2012. The IRB provided no other documents describing its procedures to FDA. These two documents do not contain all of the written procedures required under FDA's regulations. Specifically, your IRB failed to create or follow written procedures for:

- Conducting its initial and continuing review of research and for reporting its findings and action: to the investigator and the institution;
- Determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;
- Ensuring prompt reporting to the IRB of changes in research activity;
- Ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects; or
- Ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of:
 - o any unanticipated problems involving risks to human subjects or others;
 - o any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or
 - o any suspension or termination of IRB approval.

See FDA's regulations at 21 CFR 56.108(a)(1-4) and (b)(1-3).

The IRB's written response to the Form FDA 483, dated November 21, 2012, does not object to the validity of FDA's conclusion that it violated 21 CFR 56.108(a-b) and 56.115(a)(6). The response states that the IRB would revise written procedures to address these violations. and would train all staff within 30-60 days, or by January 17, 2013. Please provide these new written procedures to FDA.

2. The IRB failed to notify investigators and the institution in writing of its decision to approve or disapprove proposed research activities or of modifications required to secure IRB approval of the research activity [21 CFR 56.109(e)].

The IRB is required to notify investigators and the institution in writing of its decision to approve or disapprove proposed research, or of modifications required to secure IRB approval.

Your IRB failed to provide written communication to investigators of its decisions to approve or disapprove research studies reviewed by the IRB. The FDA investigator was told that, instead, clinical investigators were only verbally informed of IRB decisions during meetings. The IRB did not provide the clinical investigators with subsequent written notification or communication of that decision.

For the trials audited by the FDA investigator, your IRB failed to provide her with evidence of written communication between the IRB and any parties outside of the Cancer Trials Support Unit (CTSU), an organization sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials. In fact, interviews with IRB members and staff revealed that your IRB's written communication regarding these trials was limited to the certification forms that the IRB sends to the

CTSU whenever they take action with regard to a trial.

The IRB's written response to the Form FDA 483, dated November 21, 2012, does not object to the validity of FDA's conclusion that it violated 21 CFR 56.109(e). The response states that the IRB would have new written procedures to address this violation within 60 days, or by January 17, 2013. Please provide these new written procedures to FDA.

3. The IRB failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)].

An IRB shall prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions, including the number of members voting for, against, and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution. Your IRB failed to adhere to the above-stated regulations.

Our inspection revealed that the number of members abstaining is not recorded in the IRB's meeting minutes. For example, minutes of the August 21, 2012, IRB meeting indicate that Dr. **(b)(6)** and Dr. **(b)(6)** made presentations to the IRB for approval of addendums and annual renewal of various studies. Both of these physicians are IRB members. The minutes indicate the number of members voting "yes" and "no," but there is no documentation of abstentions. In order to adequately document actions taken by the IRB, the minutes should indicate the number of members abstaining (if none, document as "0"), as well as the number of members who did not vote due to a conflict of interest. IRB members with a conflict of interest may not vote or be counted towards quorum when research in which they have a conflict is being reviewed by the IRB.

The IRB's written response to the Form FDA 483, dated November 21, 2012, does not object to the validity of FDA's conclusion that it violated 21 CFR 56.115(a)(2). The response states that the IRB would have new written procedures to address this violation within 60 days, or by January 17, 2013. Please provide these new written procedures to FDA.

4. The IRB failed to ensure that basic elements of informed consent are included in the IRB-approved consent form [21 CFR 56.109(b)].

The IRB must require that information given to subjects during the informed consent process includes the fundamental elements necessary to obtain the informed, understanding, and voluntary consent of subjects in accordance with 21 CFR 50.25. These most basic components of informed consent dictate that study subjects receive at minimum:

- notice that the study involves research;
- a description of all reasonably foreseeable risks or discomforts;
- a description of any benefits that can be reasonably expected to accrue as a result of the research;
- an explanation of any appropriate alternative procedures or treatments that might be available;
- notice of the extent to which confidentiality will be maintained;
- an explanation of any compensation and/or medical treatments available if injury occurs during research involving more than minimal risk; and
- information on whom to contact both for answers to questions and in the event of a research-related injury.

See 21 CFR 50.25(a)(1-7).

Our inspection revealed that the IRB failed to ensure that the IRB-approved informed consent form for Study **(b)(4)**, "**(b)(4)**," contained adequate information about reasonably foreseeable risks or discomforts as required by 21 CFR 50.25(a)(2). As discussed below, your IRB failed to incorporate four rare but serious risks into the informed consent document (ICD) in Addendum 10 of Study Protocol **(b)(4)**, despite notification by the **(b)(4)** and discussion by the clinical investigator during the August 21, 2012, IRB meeting.

On June 18, 2012, **(b)(4)** informed the IRB that an error had been discovered in "Appendix I model informed consent document in Addendum 10 of protocol **(b)(4)**."^[1] **(b)(4)** letter warned that the following four rare but serious risks had been accidentally deleted from page 8 of the appendix to the ICD in Addendum 10 to the protocol:

- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body;
- Decrease in heart's ability to pump blood during the 'active' phase of the heartbeat (systole);
- Heart attack caused by a blockage or decreased blood supply to the heart; and
- High blood pressure of the blood vessels in the lungs.

(b)(4) noted in the letter that the forthcoming Addendum 11 would correct the mistake. However, since Addendum 11 had not yet been issued, **(b)(4)** instructed IRB personnel to ensure that, in the meantime, Addendum 10 would not be provided to study subjects without "add[ing] these risks to the informed consent document used to enroll patients at your site."

This letter did not constitute your IRB's only notification that the ICD in Addendum 10 failed to inform research subjects of four major risks of the research. During an IRB meeting, clinical investigator and IRB member Dr. **(b)(6)** "explained that an error was discovered in the informed consent for Addendum 10," and that the "[d]eleitions needed to be re-added to the consent for Addendum 10."^[2]

Despite **(b)(4)**'s instruction and the presentation by a clinical investigator who sat on your IRB during an IRB meeting, during that same meeting, Agnesian Healthcare's IRB approved Addendum 10 for Study Protocol **(b)(4)** without adding the four serious risks. The IRB should have not approved an ICD known to contain an error and should have instructed the clinical investigator to correct and resubmit the ICD for further IRB review. Failure to ensure that all of the FDA-required elements of informed consent are met prevents human subjects from being provided with enough information about a study to give effective informed consent.

The IRB's written response to the Form FDA 483, dated November 21, 2012, does not object to the validity of FDA's conclusion that it violated 21 CFR 50.25(a) and 56.109(b). The response states that the IRB would have new written procedures to address these violations within 60 days, or by January 17, 2013. Please provide these new written procedures to FDA.

5. The IRB failed to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)(1) and (4)].

An IRB is required to prepare and maintain adequate documentation of IRB activities including, but not limited to, copies of progress reports submitted by investigators and copies of all correspondence between the IRB and the investigators. The IRB failed to adhere to this requirement.

For the studies audited by FDA, your IRB's study files only included the initial protocols and ICDs, updated protocols and ICDs, and Clinical Trial Support Unit (CTSUS) IRB certification forms. From the evidence obtained, it appears that the IRB has failed to maintain any written communication between the IRB and clinical investigators of IRB decisions (as described under Item 2 of this letter) or any written documentation of any unanticipated problems or progress reports for these studies.

Additionally, the IRB has not been requiring clinical investigators to submit unanticipated problems or progress reports to the IRB. Rather, the IRB's process for receiving information with respect to ongoing research has been through communication with the CTSU.^[3]

Maintaining records, as required under the regulations, provides significant evidence of whether the procedures utilized by the IRB are adequately protecting the human subjects of the clinical investigations that the IRB is reviewing.

The IRB's written response to the Form FDA 483, dated November 21, 2012, does not object to the validity of FDA's conclusion that it violated 21 CFR 56.115(a)(1) and 56.115(a)(4). The response states that the IRB would have new written procedures to address these violations within 60 days, or by January 17, 2013. Please provide these new written procedures to FDA.

As noted above, your IRB's written response to the Form FDA 483, dated November 21, 2012, acknowledges the validity of each of the violations listed above. The response states that the IRB will develop new written procedures to address each violation. However, the response does not indicate that the draft or final procedures will be provided to FDA. In addition, the IRB's written response to the Form FDA 483 is inadequate to address these violations because it does not describe any process that the IRB will use to train and educate IRB members, staff, and clinical investigators with respect to its new written procedures. Without this information, FDA cannot conduct a proper evaluation of the proposed corrective and preventive action's potential ability to prevent the recurrence of these or similar violations in the future.

This letter is not intended to be an all-inclusive list of deficiencies for the protocols reviewed and approved by the IRB. It is your responsibility to ensure that Agnesian Healthcare IRB's practices and procedures comply fully with all applicable statutes and regulations.

Within fifteen (15) business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Your written response should include any documentation necessary to show that full and adequate correction will be achieved. Please include the projected completion dates for each action to be accomplished. Failure to explain the violations noted above adequately and promptly may result in regulatory action without further notice.

We recommend that you visit the following FDA Web page for information on human subject protections that may assist you in your efforts to bring the IRB into compliance with FDA regulations

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

We appreciate the cooperation shown to the FDA Investigator, Ms. Denise Burosh, during the inspection. If you have any questions, please contact Catherine Parker, R.N., at 301-796-5553; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Catherine Parker, R.N.
Team Lead, Human Subject Protection Branch
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5247
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

{See appended electronic signature page}

Thomas N. Moreno, M.S.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Cc: Mr. James P. Mugan
IRB Chairman
Agnesian Healthcare
430 East Division Street
Fond du Lac, WI 54935

[1] Letter from **(b)(4)**, **(b)(4)**, to **(b)(4)** Site Staff Regarding Deletion of 'Rare but Serious' Risks in Addendum 10 **(b)(4)** Model Informed Consent (June 18, 2012).

[2] Meeting Minutes of the Agnesian Healthcare Institutional Review Board signed by Chairperson James Mugan (Aug. 21, 2012).

[3] See discussion *supra* Citation 2, Paragraph 3.

Page Last Updated: 03/29/2013

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